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PATENT

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In re application of:

Antoniou *et al.*

Serial No.: **09/247,054**

Group Art Unit: **1632**

Filed: **February 9, 1999**

Examiner: **A-M Baker**

For: **SELF-REPLICATING VECTORS CONFERRING TISSUE-SPECIFIC GENE EXPRESSION**

I, **Doreen Yatko Trujillo**, Registration No. **35,719**, certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On March 26, 2002

Doreen Yatko Trujillo

Doreen Yatko Trujillo
Registration No: 35,719

Box AF
Assistant Commissioner
for Patents
Washington, D.C. 20231

Dear Sir:

DECLARATION PURSUANT TO 37 C.F.R. §1.132

I, Michael Antoniou, PhD, do hereby declare as follows:

1. I am an inventor of the subject matter of U.S. Application Serial No. 09/247,054, filed February 9, 1999 ("'054 application"), for which Cobra Therapeutics Limited is the Assignee.

2. I fully acknowledge the presence within the prior art of Epstein-Barr virus (EBV)-based replicating episomal vectors (first described by Yates JL, Warren N, Sugden B. Stable replication of plasmids derived from Epstein-Barr virus in various mammalian cells. Nature 1985; 313: 812-815) and locus control regions (LCRs; originally known as dominant control regions and first described by Grosveld F, Blom van Assendelft GB, Greaves DR, Kollias G.

"Position-independent high level expression of the human β-globin gene in transgenic mice." Cell 1987; 51: 975-985). Many more examples of replicating episomal vectors (REVs) and LCRs could have been quoted in addition to those sited by the Examiner and which we openly and freely refer to in our application. Our application does not claim invention of the utility of independent use of either REVs or LCRs. We claim the totally novel and successful use of *combining* these two systems, which as described below, could not have been predicted based on the published and accepted properties of REVs and LCRs at the time of filing. LCRs were discovered in the laboratory of Prof Frank Grosveld in 1987 during the time when I was under his employ as a post-doctoral research fellow. I have worked on the basic molecular biology and biotechnological utility of LCRs from the time of their discovery, both in collaboration with Prof Grosveld and independently since establishing my own research group in 1994. As a result I am intimately aware of the properties of LCRs. I can therefore categorically state that all our own published work as well as that of many others clearly suggested that LCRs are *only* capable of exerting their transcriptional activating properties when *integrated* within the host cell genome. Consequently, there was *no* expectation that LCRs would function from within REVs as described in this application.

3. The prevailing opinion that LCRs could *not* function from within REVs, is further highlighted by the long lapse of time between the invention of these two systems and their eventual combination. The description of EBV-based REVs was, as mentioned above, in 1985 (Yates JL et al., Nature 1985; 313: 812-815) whereas LCRs were discovered in 1987 (Grosveld F et al., Cell 1987; 51: 975-985). However, our priority filing date for the utility of LCRs within REVs was in August 1996. The gap of *9 years* between the discovery of LCRs and the demonstration of their utility within REVs, was due to the overwhelming weight of opinion based on published results at the time suggesting that these two systems were incompatible. Indeed, when we conducted the first experiments, the expectation was that LCRs would *not* be able to exert their function from within REVs. The successful outcome of our experiments was therefore unexpected and surprising. I hope that this is helpful to the Examiner in clarifying that the use of LCRs within REVs went against the available experimental evidence at the time of filing and that it clearly constitutes a conceptual leap and inventive step.

4. I declare that all statements made herein are of my own knowledge true and statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

MAntoniou 25/3/02

Michael Antoniou, PhD. Date